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Medical Comorbidity of Attention-Deficit/Hyperactivity Disorder in US Adolescents

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Abstract

Understanding patterns of medical comorbidity in attention-deficit/hyperactivity disorder (ADHD) may lead to better treatment of affected individuals as well as aid in etiologic study of disease. This article provides the first systematic evaluation on the medical comorbidity of ADHD in a nationally representative sample (National Comorbidity Replication Survey–Adolescent Supplement; N = 6483) using formal diagnostic criteria. Survey-weighted odds ratios adjusted for demographics, additional medical, and mental disorders were calculated for associations between ADHD and medical conditions. Models adjusted for demographics revealed significantly increased odds of allergy, asthma, enuresis, headache/migraine, and serious stomach or bowel problems. After adjusting for comorbidity, across the medical conditions, enuresis and serious stomach problems were the strongest correlates of ADHD. These findings confirm the pervasive medical comorbidity of ADHD reported in previous clinical and community-based studies. The intriguing salience of enuresis and serious stomach or bowel conditions may also provide an important clue to multisystem involvement in ADHD.

Keywords

ADHD, comorbidity, enuresis, National Comorbidity Replication Survey–Adolescent Supplement, *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition*

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Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset neurodevelopmental disorder with a lifetime prevalence of 5.9% to 8.7%.[1-3] ADHD can negatively impact a child's family, social, and academic life. The clinical heterogeneity of its manifestations has been studied both in clinical and community samples,[4-22] revealing that individuals who suffer from ADHD are also likely to experience an array of comorbid medical and psychiatric conditions at a higher than expected frequency. Comorbidity has been shown to potentiate the impact of ADHD on a child's academic,[23-26] social,[27-29] and behavioral[30-32] functioning. Chronic medical conditions reported with increased frequency among adults and children with ADHD include epilepsy,[33] headaches/migraine,[22,34] atopic diseases and asthma,[34-39] enuresis,[40-45] and gastrointestinal disorders.[22,42,46,47] While patterns of comorbidity of ADHD with other psychiatric disorders have been well documented,[9,10,12,14,21,22,42,46-50] no population-based study to date has systematically conducted a comprehensive multisystem evaluation of ADHD comorbidity using formal diagnostic criteria.

Understanding patterns of medical comorbidity in ADHD may lead to better treatment of affected individuals as well as aid in etiologic study of disease. Comorbidity can significantly influence delivery of medical care as it may confound diagnosis and pose special therapeutic challenges. Furthermore, knowledge of common biologic systems involved would not only help physicians provide better care for their patients but may also provide some clues regarding sources of heterogeneity of ADHD. The objective of this study was to examine the association between ADHD and a range of chronic medical conditions in a nationally representative sample of US adolescents.

Methods

Sample

As previously reported in more detail, the National Comorbidity Survey-Adolescent Supplement was conducted in the continental United States between February 2001 and January 2004.[51] Adolescents aged 13 to 18 years were interviewed face to face in a dual sampling frame in which one sample was recruited from the

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households and the other from a representative sample of schools in the same communities as these households.[52] The overall adolescent response rate was 75.6%, for a total of 10 148 completed interviews (10 123 after the elimination of 25 nonstudents respondents). One parent or guardian who was most knowledgeable to the participating adolescent's health was mailed a parent self-administered questionnaire (PSAQ) to collect information on participating adolescent's developmental history, physical and mental health, and other family- and community-level factors. The response rate to the PSAQ was 63.0%. The conditional parent response rate given per adolescent response did not differ substantially between the household sample and school sample.

The data were weighted to adjust for the differential probability of selection of adolescents within the school and household samples for differential nonresponse, and for residual differences between the sample and US population on the cross-classification of sociodemographic characteristics. This study focuses on 6483 adolescent-parent pairs for whom data were available from both adolescent interviews and parent PSAQs. All recruitment and consent procedures were approved by the Human Subjects Committees of Harvard Medical School and the University of Michigan.

Measures

Attention-deficit/hyperactivity disorder and subtypes. A computerized algorithm was applied to generate ADHD diagnosis variables using diagnostic information obtained from parents in PSAQ. A diagnosis of ADHD was based on *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* criteria.[53] Adolescents met lifetime criteria for ADHD if parent reported the following: criterion A, 6 symptoms of either inattention and/or hyperactivity-impulsivity; criterion B, symptoms causing impairment present before age 7 years; criterion C, some impairment in at least 2 settings (at school or work and at home); and criterion D, clinically significant impairment in social, academic or occupational functioning. The diagnostic hierarchy rule (criterion E) was not operationalized. Adolescents were classified as ADHD inattentive subtype if parent reported predominantly inattention symptoms; or as ADHD hyperactive/impulsive subtype if they endorsed predominantly hyperactivity/impulsivity symptoms; or as ADHD combined subtype if they met symptom criterion A for both inattention and hyperactivity/impulsivity.

Demographic and mental correlates of ADHD. Socio-demographic variables included adolescent age (mean = 15.2y), sex (48.7% female, 51.2% male), race/ethnicity (65.5% non-Hispanic white, 15.1% non-Hispanic black, 14.4% Hispanics, and 5.0% other race), parental highest education attainment (12.3% less than high school, 29.3% high school graduation, 21.3% some college, and 37.4% college graduation).

Other *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* disorders were assessed in the survey by using a modified version of the World Health Organization Composite International Diagnostic Interview, a fully structured interview administered by trained lay interviewers. Lifetime disorders assessed by the Composite International Diagnostic Interview include anxiety disorders, behavior disorders, mood disorders, and substance use disorders. Adolescent reports were used to assess diagnostic criteria for emotional disorders and substance use disorders, while information from the parent and the adolescent were combined at symptom level for behavior disorders. A symptom was considered present if reported by either the parent or adolescent. Definitions of these psychiatric disorders adhered to *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* criteria.

Medical conditions. The parent of each participating adolescent was asked questions about the adolescent's physical and mental health, described previously in more detail.[54] The physical health section included questions about lifetime presence of medical conditions affecting a range of bodily systems, including neurologic disorders (seizures/epilepsy, severe headaches or migraines), heart problems, inflammatory conditions (asthma, allergies), skin problems (acne, psoriasis, eczema), and stomach trouble (such as gastritis, ulcers). Lifetime enuresis was considered present if the parent reported the adolescent stopped bed-wetting after the age of 5 years. Body mass index was calculated from adolescent-reported height and weight using weight (kg)/height(m)^2. A dichotomized obesity status was defined if the body mass index equals to or higher than the 95 percentile based on Centers for Disease Control and Prevention age- and sex-specific growth curve. Perceived excellent physical health was defined as a parent-reported physical health rating of 10 on a scale of 0 to 10.

Statistical Analyses

All statistical analyses were completed with the SUDAAN software package (version 10) using the Taylor series linearization method to take into account the complex survey design. Cross-tabulations were used to estimate percentages of ADHD and its subtypes by sociodemographic strata and clinical features as well as prevalence of mental comorbidity of ADHD and its subtypes. Means were used for continuous clinical features such as the number of inattentive or hyperactive symptoms. Survey-weighted multivariable logistic regression analysis was performed to examine the association between demographic correlates, medical comorbidity of ADHD and its subtypes, controlling for potential confounders including sex, age, race/ethnicity, parent education, and other medical and mental disorders. Multivariable logistic regression coefficients and standard errors were exponentiated to generate adjusted odds ratios and 95% confidence intervals for ease of interpretation. The design-adjusted Wald χ^2 test was used to examine group differences statistically. Significance was based on 2-sided tests evaluated at the level of .05.

Results

Table 1 presents the prevalence of comorbid medical conditions by ADHD and ADHD subtype affected status. Allergies/hay fever was the most prevalent condition among ADHD cases (45.8%, SE: 3.9), with other comorbid conditions ranging from 45.8% for allergies or hay fever to 3.9% for seizures or epilepsy. Rates of all of these comorbid conditions were elevated compared to those of youth without ADHD, with statistical significance of these differences shown in Table 2. With respect to ADHD subtypes, prevalence of allergies/hay fever was higher among inattentive subtype cases (49.7% vs 39.0%), asthma among hyperactive/impulsive subtype cases (40.3% vs 19.6%), and headaches/migraine among combined subtype cases (40.1% vs 31.6%). Testing group differences among subtypes revealed that a significantly higher proportion of adolescents affected with the hyperactive/impulsive subtype had asthma compared to inattentive and combined subtypes (40.3%, 21.7% and 24.7%; Wald $\chi^2_2 = 3.6$, $P = .001$). Not shown here, females with ADHD had greater rates of allergies/asthma and headaches/migraine than males, whereas males with ADHD had greater rates of obesity.

Table 1. Prevalence of Comorbidity of Lifetime Attention-Deficit/Hyperactivity Disorder (ADHD) With Medical Conditions.

	Subtype of ADHD, % (SE)				
	Any type	Inattentive	Hyperactive/impulsive	Combined	No ADHD
	n = 550, 8.7%	n = 196, 3.7%	n = 84, 1.7%	n = 270, 3.8%	n = 5933
Medical condition					
Allergies or hay fever[c,p]	45.8 (3.9)	49.7 (5.1)	42.8 (11.1)	43.3 (4.4)	39.0 (1.3)
Asthma[c,p]	26.3 (3.2)	21.7 (4.5)	40.3 (7.4)	24.7 (4.9)	19.6 (0.9)
Chronic pain[c]	7.7 (2.0)	10.8 (3.7)	6.6 (4.4)	5.2 (1.9)	5.8 (0.4)
Enuresis[p]	19.4 (2.5)	18.3 (4.2)	14.4 (6.4)	22.5 (3.2)	9.4 (0.4)
Epilepsy or seizure disorder[c,p]	3.9 (1.6)	6.9 (3.9)	1.6 (1.1)	2.0 (0.8)	2.4 (0.3)
Headaches or migraine[c,p]	37.3 (3.5)	39.1 (6.4)	26.6 (9.0)	40.1 (4.1)	31.6 (0.9)
Heart problems[c,p]	6.5 (1.5)	7.8 (2.6)	2.4 (1.1)	6.9 (2.5)	4.4 (0.4)
Obesity[c]	22.3 (3.6)	21.4 (4.7)	29.0 (8.9)	20.2 (3.5)	14.6 (0.8)
Serious stomach or bowel problems[c,p]	10.4 (1.7)	10.7 (2.8)	9.1 (4.9)	10.6 (2.1)	5.6 (0.6)
Severe acne or other skin problems[c,p]	36.5 (3.5)	34.4 (6.4)	30.4 (8.9)	41.0 (3.5)	32.0 (1.1)

Medical conditions using a checklist based on adolescent (c) and/or parent (p) reports.

Table 2. Associations of Lifetime Attention-Deficit/Hyperactivity Disorder (ADHD) and Medical Conditions.

	1. aOR (95% CI)	2. aOR (95% CI)	3. aOR (95% CI)
Medical condition			
Allergies or hay fever[c,p]	1.39 (1.01-1.91)*	1.21 (0.86-1.70)	1.34 (0.91-1.98)
Asthma[c,p]	1.49 (1.04-2.14)*	1.21 (0.82-1.78)	1.17 (0.80-1.71)
Chronic pain[c]	1.38 (0.75-2.55)	1.18 (0.66-2.10)	1.19 (0.63-2.23)
Enuresis[p]	2.04 (1.41-2.95)***	1.85 (1.26-2.70)*	1.56 (1.06-2.29)*
Epilepsy or seizure disorder[c,p]	1.62 (0.68-3.87)	1.25 (0.59-2.62)	1.13 (0.51-2.54)
Headaches or migraine[c,p]	1.46 (1.07-1.98)*	1.22 (0.90-1.65)	0.89 (0.65-1.24)
Heart problems[c,p]	1.44 (0.71-2.89)	1.00 (0.51-1.96)	0.94 (0.50-1.76)
Obesity[c]	1.39 (0.92-2.09)	1.16 (0.75-1.79)	1.18 (0.70-2.01)
Serious stomach or bowel problems[c,p]	2.06 (1.33-3.19)***	1.64 (1.00-2.68)*	1.33 (0.83-2.11)
Severe acne or other skin problems[c,p]	1.23 (0.91-1.67)	1.12 (0.82-1.54)	0.94 (0.67-1.31)

Medical conditions using a checklist based on adolescent (c) and/or parent (p) reports. Models using medical conditions (variables in the first column) as outcomes in logistic regression models, 1 condition at a time, ADHD disorder status as predictor: 1. Adjusted odds ratio (aOR) controlling for demographics only (sex, age, race/ethnicity, parental education). 2. aOR also adjusted for other medical disorders. 3. aOR fully adjusted (ie, adjusted for demographics, other medical disorders, and other *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* disorders).
*$P < .05$. ***$P < .001$.

Associations between medical conditions and ADHD based on logistic regression models that controlled for sex, age, race/ethnicity, and parent education are presented in Table 2. ADHD cases were more likely to be affected by allergies/hay fever (aOR[1]: 1.39, 95% CI: 1.01-1.91), asthma (aOR[1]: 1.49, 95% CI: 1.04-2.14), enuresis (aOR[1]: 2.04, 95%CI: 1.41-2.95), headaches/migraine (aOR[1]: 1.46, 95% CI: 1.07-1.98), and serious stomach or bowel problems (aOR[1]: 2.06, 95% CI: 1.33-3.19). The second column presents the odds ratios after simultaneous adjustment for presence of other medical conditions. Findings revealed that enuresis (aOR[2]: 1.85, 95% CI: 1.26-2.70) and stomach/bowel problems (aOR[2]: 1.64, 95% CI: 1.00-2.68) had the strongest associations with ADHD. The third column of Table 2, which presents the results after further adjustment for the presence of other *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* mental disorders, shows that enuresis was the only medical condition that remained significantly associated with ADHD (aOR[3]: 1.56, 95% CI: 1.06-2.29). When age of bed wetting threshold was increased from current 5y to 7y, prevalence of enuresis dropped from 10.3% (SE = 0.4) to 7.2% (SE = 0.5), however the association of ADHD and enuresis became stronger (aOR[3]: 1.67, 95% CI: 1.05-2.65). ADHD parents were approximately twice as likely to report less than excellent physical health rating compared to parents of unaffected adolescents. This association remained significant under all adjusted models (aOR[1]: 2.03, 95% CI: 1.45; aOR[2]: 1.78, 95% CI: 1.28-2.46; aOR[3]: 1.79, 95% CI: 1.24-2.58). The authors further examined whether the patterns of comorbidity differed between ADHD cases who did and did not receive medication/treatment. Of 550 children with ADHD, 345 reported ever receiving medication/treatment for ADHD and 205 did not receive treatment. The authors found that the associations between ADHD and examined medical conditions among ADHD cases who were not treated did not reach statistical significance. The observed overall comorbidity patterns between ADHD and medical conditions were largely determined by those ADHD cases who received medication/treatment.

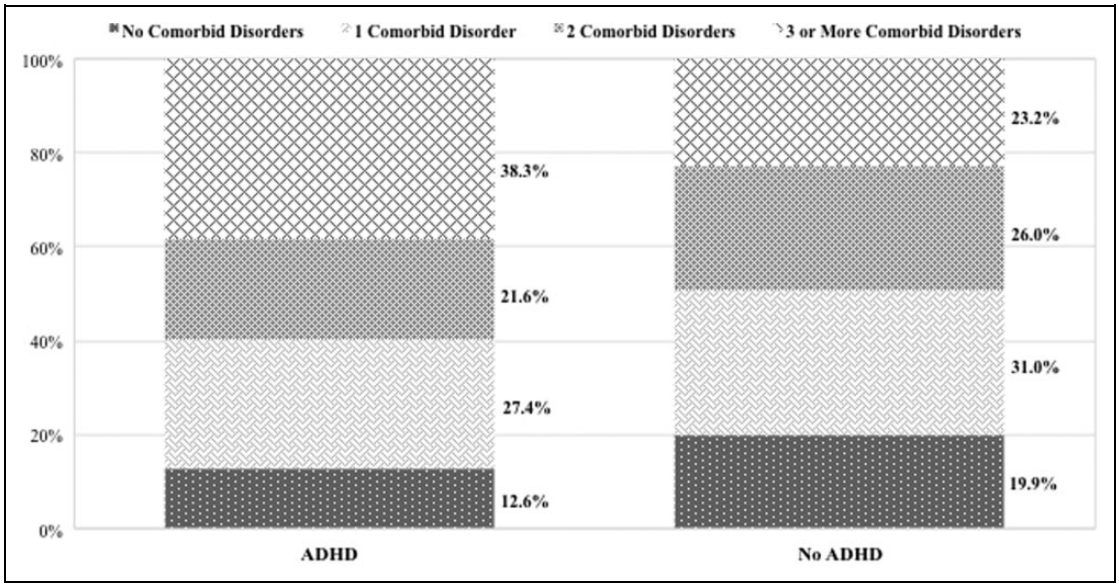

Figure 1. The number of comorbid nonpsychiatric medical disorders in those with and without attention deficit/hyperactivity disorder (Wald chi-square = 40.9, df = 3, $P < .0001$). Data are from the National Comorbidity Replication Survey–Adolescent Supplement (N = 6483).

Figure 1 illustrates proportions of number of medical conditions present among ADHD cases and noncases. Over 87% of adolescents with ADHD reported having at least 1 comorbid medical condition, and nearly 40% have 3 or more comorbid medical conditions. Proportions of comorbidity among youth with ADHD are significantly higher than those without ADHD (Wald $\chi^2_3 = 40.9$, $P < .001$). Females also tended to have more comorbid disorders than males.

Discussion

This study provides compelling evidence regarding pervasive comorbidity of ADHD with diverse medical conditions in this nationally representative sample. There was a significantly greater prevalence of specific chronic medical conditions as well as an increased number of medical conditions among those youth with ADHD compared to their unaffected counterparts. These results confirm those of previous clinical studies of ADHD comorbidity that have reported increased frequencies of allergies and asthma,[55,56] headaches and migraine,[57,58] enuresis,[40,41,43,59,60] and gastrointestinal or bowel problems.[47] The authors also confirm findings of prior community studies that document poorer health in general among those with ADHD,[2,18,22,34,61,62] as well as associations with specific medical conditions including allergies and asthma,[22,34-36,39,63-65] headaches/migraine,[22,34,66] enuresis,[42,44,45,67] and gastrointestinal/bowel problems.[22,46,67] The confirmation of comorbidity in the general population demonstrates that the associations are not an artifact of clinical samples that are characterized by more severe, comorbid conditions. The results also extend those on comorbidity of a range of medical conditions with ADHD from a recent nationally representative US sample that demonstrated the specificity of comorbidity with respect to comorbid learning disability and/or developmental disorders.[22] These patterns of comorbidity may provide insight into sources of clinical and etiologic heterogeneity of ADHD, as well as the associated medical conditions, and may have important relevance to the treatment of affected youth.

The salience of enuresis in the multivariate models, that confirms the authors' earlier evaluation of medical comorbidity in the National Health and Nutrition Examination Survey[44] suggests that enuresis may provide an index of the underlying pathways to at least some subtypes of ADHD. These pathways may result from a common mechanism that impacts multiple systems. The maturational delay and/or dysfunction of the frontal lobe circuitry that have been implicated in both enuresis[68,69] and ADHD[70,71] may comprise a common etiologic feature that could explain the significant comorbidity of the two. The links between ADHD with allergies and asthma may also implicate the role of common immunologic regulatory factors in neurodevelopmental disorders.[72]

Implications of Comorbidity

This pervasive comorbidity should be considered in the evaluation and treatment of youth with ADHD. There has been increasing scrutiny of the health care system with the passage of health care reform. Indeed, the development of evidence-based methods to improve the quality of care in subgroups most at risk is the chief goal of the below-cited Synthesis Project on mental disorder and medical comorbidity.[73] Although this project focuses on adults, there has been an increasing awareness among clinicians of the need for better integration of mental health and medical specialty care in children,[74] and both local and national efforts are underway.[75] Clinicians' awareness of comorbidity patterns can encourage evaluation and diagnosis for associated conditions, thus facilitating appropriate treatment and minimizing potential secondary negative impact of

treatment of ADHD on these other conditions. To date, there is a dearth of systematic evidence for the treatment of ADHD in the context of comorbid medical or mental disorders. These findings suggest that such research is imperative. Documentation of comorbidity patterns may also provide insight into sources of etiologic and phenotypic heterogeneity of ADHD. These findings provide intriguing clues that ADHD comorbid with enuresis could be an index of immaturity of neural maturation, whereas associated gastrointestinal problems could potentially comprise a signal of underlying inflammatory processes, or impaired communication between the brain and bowel.[47] Future studies of these potential pathways are indicated.

Strengths and Limitations

The strengths of this study include the large and nationally representative sample of adolescents and the breadth of correlates of chronic medical conditions included in the survey. It is the first population-based study of ADHD and its subtypes to investigate comorbidity with a range of medical conditions among adolescents in a nonclinical sample using full *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* diagnostic criteria. Limitations of this study include its cross-sectional nature and the fact that the findings of comorbidity are necessarily correlative and cannot address causality. It would be interesting to assess the temporal sequence of the associated disorders to evaluate the effect of disease progression and medication use over time as well as to permit the design of better strategies for prevention, management, and understanding of biological processes involved in disease etiology. In addition, this study relied on parent report of medical conditions rather than confirmed diagnoses; however, parent reports have been shown not only to be a reliable measure of child general health status,[76] but also of a clinician confirmed ADHD diagnosis.[77] Several studies have also supported the use of parent rather than child reports based on the poor validity of child-reported externalizing symptoms.[78,79] Nonetheless, results should be interpreted with caution as they cannot effectively rule out confounds with a primary diagnosis. When stratifying results of this study by use of medication/treatment, the associations between ADHD and nonpsychiatric medical conditions remained significant only among adolescents with ADHD who used medication/treatment. ADHD treatments can include a variety of stimulant and nonstimulant drugs. Importantly, enuresis has not been reported as a significant side effect of any stimulant. Thus, while the authors are unable to rule out the possibility that enuresis is a side effect of medication use, it is likely these findings are a result of the fact that the children who received medical treatment for their ADHD have a more clinically severe disorder, which may in turn be related to higher levels of comorbidity with enuresis. Cohen-Zion and Ancoli-Israel[80] performed an extensive review of 47 research studies to describe the relationship between sleep and ADHD, and to provide information on the effect of stimulant medication on sleep. The compared studies, which had included nonmedicated ADHD and stimulant medicated ADHD, found that parasomnias, such as nocturnal enuresis, are more common in children with ADHD (who are not medicated) than controls. They suggest that the high prevalence of enuresis may be related to the etiology of ADHD. Nocturnal enuresis is known to occur in non–rapid eye movement sleep (and in some cases specifically slow wave sleep or deep sleep) and may be associated with higher arousal thresholds. Dysfunction of the noradrenergenic system known to be involved in arousal has also been hypothesized to be associated with the etiology of ADHD.[80] Finally, while it would be interesting to analyze these data utilizing the new *Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition* criteria for ADHD,[81] which includes increasing the age of onset of the disorder to age 12 from age 7, the measures used prohibit the assessment of accurate ADHD prevalence numbers for those over the age of 7.

Conclusion

The lines between mental health and physical health are becoming increasingly blurred as the understanding of common physiologic processes affect multiple organ systems. The current finding regarding pervasive medical comorbidity of ADHD highlights the complex interplay between physical and mental health. Future research should investigate medical comorbidity as a source of heterogeneity of ADHD and systematically incorporate comorbidity in treatment planning.

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Author Contributions

NDJ wrote the first draft of the manuscript and contributed to the editing process. BKS wrote sections of the first draft of the manuscript and contributed to the editing process. TML contributed to the editing process. JLV contributed to the editing process. JPH wrote sections of the first draft, contributed to the editing process, and had full access to all of the data, completing all analyses. KRM oversaw completion of the manuscript, contributing to all parts of the writing and data analyses.

Declaration of Conflicting Interests

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Ethical Approval

The Human Subjects Committees of both Harvard Medical School and the University of Michigan approved these recruitment, consent, and field procedures.

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